



# Impact of Maternal Endocrine Health on Foetal Development and Pregnancy Outcomes

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## Abstract

Maternal endocrine health is an essential predictor of favourable pregnancy outcomes, regulating both foetal development and maternal well-being. Pregnancy relates to significant hormonal changes that promote maternal-foetal connection and foetal growth. Maternal endocrine disturbances, whether caused by pre-existing illnesses or pregnancy-induced problems, can harm both the foetus and the mother. This review delves into the physiology and adaptations of the maternal endocrine system, concentrating on major organs such as the thyroid, pancreas, adrenal glands and placenta. The pathogenesis of gestational diabetes and thyroid dysfunctions and their effects on mother and foetal health. During pregnancy, it impairs foetal neurodevelopment, growth and congenital malformations, often caused by hormonal imbalances and disruptors. Polycystic ovary syndrome (PCOS), though not a gestational disorder, is a major preconception risk factor for infertility, gestational diabetes and adverse perinatal outcomes. These endocrine perturbations collectively contribute to an elevated risk of obstetric complications, including preterm birth, stillbirth and neonatal morbidity. These endocrine perturbations lead to an elevated risk of obstetric complications, including preterm birth, stillbirth and neonatal morbidity. Furthermore, environmental and epigenetic factors are evaluated in mother-foetus health due to their potential transgenerational consequences. Future research directions include combining personalized medicine, omics technologies and artificial intelligence to improve maternal-foetal outcomes. Improved diagnosis accuracy, treatment efficacy and preventative care will also contribute to the achievement of numerous Sustainable Development Goals, such as improving health and well-being, eliminating health-care disparities and supporting maternal-foetal health innovation. This study highlights the critical need to increase global efforts to promote maternal-foetal endocrine research and treatment.

**Key words:** Maternal health; Child health; Infant health; Endocrine system; Pregnancy outcome; Healthcare; Organisational innovation.

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## Introduction

The endocrine health of the mother significantly influences foetal growth and pregnancy outcomes.<sup>1</sup> The maternal endocrine environment is

responsible for supplying essential substrates for foetal development and regulating the time and method of their delivery.<sup>2</sup> Furthermore, the foe-

tal endocrine system initiates development early in gestation, facilitating the regulation of several physiological processes essential for growth and adaptation to life outside the womb.<sup>3</sup> The stimulation of the hypothalamic-pituitary-adrenal (HPA) axis near the conclusion of gestation results in heightened cortisol production, essential for lung maturation and metabolic preparedness at delivery.<sup>4</sup> Research shows that poor maternal endocrine health might have enduring repercussions on both the mother and child. For example, gestational diabetes mellitus (GDM) demonstrates how hormonal imbalances during pregnancy can impact outcomes, with GDM connected to a higher chance of macrosomia and an increased risk of metabolic problems in the offspring.<sup>5</sup>

The endocrine system, responsible for developing hormones that govern numerous physiological processes, is crucial for sustaining a normal pregnancy. Hormonal changes during pregnancy, both normal and pathological, can profoundly impact maternal health, foetal growth and long-term results for both mother and child.<sup>6</sup> Endocrine disrupting chemicals (EDCs) are exogenous compounds that can interfere with our biological processes such as foetal organ development, mother's immunity and metabolism by disrupting the endocrine system. They can disturb production, transportation, metabolism, which are responsible for maintenance and regulation of development processes.<sup>7</sup> Hormones have a vital function in the regulation of foetal growth, maternal consumption of suitable macro and micronutrient supplements and acquiring fresh air free from pollution, allergies and toxic gasses undoubtedly aids from altering hormones. More recently, several experts began researching more closely the consequences that chemicals extensively diffused in the environment might reflect on both the mother and the foetus health state.<sup>8</sup> Moreover, EDCs might contribute to the emergence of serious gestational disorders like gestational diabetes in pregnancy, foetal growth restriction (FGR), preeclampsia (PE).<sup>9</sup> In reality, epidemiological studies have actually shown that variations in maternal and placental hormone levels during pregnancy may increase the risk of various health issues for children later on, such as neurodevelopmental impairment, endometriosis, prostate and breast cancer, as well as polycystic ovary syndrome (PCOS).<sup>10</sup> Interestingly, minor alterations in prenatal hormones can affect long-term health is understudied.

The review emphasises the need for modern diagnostic methods, including biomarkers, imaging techniques and non-invasive prenatal testing, in detecting and monitoring these illnesses. This multifaceted approach to tackling the problems of endocrine disorders in pregnancy involves preconception care, lifestyle changes, pharmaceutical therapies and novel methods such as gene editing and regenerative medicine and focus on the importance of adaptation to good endocrine health from prenatal to the postnatal period to reduce the pregnancy complications and to peer review how important is the balancing of hormones without disruption that could cause severe health issues even after the postpartum period in women.

## Maternal endocrine system: physiology and adaptations

Throughout pregnancy, the mother's endocrine system undergoes significant physiological changes in order to nourish the growing foetus and get her ready for delivery. It undergoes major physiological modifications throughout pregnancy to facilitate foetal growth and ensure mother health.<sup>11</sup> Human chorionic gonadotropin (hCG), which is produced by the placenta that aids in maintaining the corpus luteum, which is necessary for progesterone synthesis in the early stages of pregnancy, is one of the hormones that can be observed playing important functions throughout the pregnancy period.<sup>12</sup> Progesterone stops uterine contractions and creates a good environment for the growing embryo. As pregnancy advances, oestrogen levels rise, encouraging uterine development and boosting blood flow. Additionally, the placenta secretes human placental lactogen (hPL), which improves maternal insulin resistance to guarantee a continuous glucose supply for the foetus. This adaptation leads to raised maternal blood glucose levels while boosting lipolysis for energy demands.<sup>13</sup> The endocrine alterations also influence other systems; for instance, greater levels of thyroid hormones boost embryonic brain development, while adjustments in renal function enhance waste elimination. Overall, these hormone alterations are crucial for supporting the growing foetus and preparing the woman for birthing.

## Hormonal regulation of pregnancy: a systemic perspective

The maternal genome and environment have an influence in foetal growth and development. Maternal characteristics such as height, weight and dietary consumption during pregnancy can considerably impact foetal development. Maternal restriction, or the restricted ability of the uterus to sustain foetal growth, is a key element in determining foetal size.<sup>14</sup> Maternal food, caloric intake and metabolic function are all critical in delivering nutrients to the foetus via the placenta. Specific nutrients including protein, folic acid, iron and the antioxidant vitamin A have been found to affect foetal development, with supplementation in undernourished women resulting to higher birth weight.<sup>15</sup> Maternal dietary intake, particularly in early pregnancy, has the largest influence on the size at delivery. Increased uterine blood flow is required to fulfil the metabolic demands of the expanding uterus, placenta and baby.

A very active endocrine organ, the placenta is essential to the development of pregnancy and the adaptation of the mother's immunological, endocrine and metabolic systems. The placenta's endocrine activity is controlled by the syncytiotrophoblast, which surrounds the blastocyst after implantation.<sup>16</sup> Through the intervillous gap, it releases hormones such as hCG into the mother's bloodstream. However, extravillous trophoblast plugs limit the flow of maternal blood via the intervillous gap during the first trimester, which restricts the release of placental proteins and hormones into the mother's circulation.<sup>17</sup> The trophoblast plugs break down during pregnancy, increasing maternal blood flow and the systemic release of placental hormones and bioactive compounds correspondingly.<sup>18</sup> Foetal sex impact on glucose metabolism have been reported differently by several cohorts. For example, some studies found that pregnancies with males had higher levels of insulin resistance, whereas pregnancies with girls showed comparable or even higher levels of resistance.<sup>19</sup> These disparities might result from variations in participant attributes including race and body mass index (BMI).

Thyroxin is essential for the foetus's neural development, even though the foetal thyroid gland does not function until the second trimester of pregnancy.<sup>20</sup> In order to ensure that the baby will have a consistent supply of thyroxin throughout

the early stages of pregnancy, the mother's T3 and T4 levels should be raised. During the second trimester of pregnancy, human placental lactogen, prolactin and cortisol levels also increase. These hormones reduce the peripheral absorption of glucose and increase the mother's insulin resistance since they are anti-insulin.<sup>21</sup> This ensures that glucose will always be available to the foetus. The mother switches to an alternative lipid-based energy source. Increased lipolysis results in higher levels of free fatty acids in the plasma, which act as a substrate for maternal metabolism. Because ketogenesis may result from the breakdown of lipids during pregnancy, there is an increased risk of ketoacidosis.<sup>22</sup> Progesterone reduces systemic vascular resistance, which decreases diastolic blood pressure throughout the first and second trimesters of pregnancy. As a consequence, the cardiac output increases by around 30 to 50 %. Pregnancy-related high blood pressure may be a sign of pre-eclampsia. Water retention and elevated sodium levels are caused by the activation of the renin-angiotensin-aldosterone system (RAAS) during pregnancy.<sup>23</sup> This suggests that the total volume of blood has increased. During pregnancy body adapts to different physiological conditions as a result GFR rises by around 50–60 % as a result of increases in renal plasma flow brought on by pregnancy-related increases in cardiac output. As a consequence of increased renal excretion during pregnancy, urea and creatinine levels will be lower. Progesterone affects the system that collects urine, which relaxes the muscles in the bladder and causes the ureter to become hydroureter.<sup>24</sup> A woman is at risk for pyelonephritis and urinary tract infections (UTIs) due to urinary stasis caused by these two changes (Table 1).

## Key endocrine organs in pregnancy (thyroid, pancreas, adrenal glands, placenta)

Triiodothyronine (T3) and thyroxine (T4) are the two main thyroid hormones that are necessary for the healthy development of the foetus's brain and nervous system throughout pregnancy. Since the foetus's own thyroid does not start to operate until around 12 weeks of gestation, it is completely dependent on the thyroid hormones of the mother throughout the early stages of pregnancy.<sup>33</sup> Elevated levels of oestrogen and hCG can stimulate synthesis of thyroid hormone. Because hCG can mimic thyroid-stimulating hormone (TSH), it can reduce TSH levels while increasing

**Table 1:** Endocrine adaptations in body during pregnancy period

Physiological conditions	During gestation			Postpartum		Ref
	1st trimester	2st trimester	3st trimester	Early (0-2 months)	Late (2-6 months)	
Vascular resistance	Decreases for vasodilation effects	Decreases	Remains low	Increases rapidly	Normal levels	[25]
Heart rate	Rises 10-15 bpm	Increases upto 100bpm	Remains elevated	Gradual decrease	Decreases	[26]
Cardiac output	Week 8 increases up to 50 %	Minimal rise	Remains elevated	Increases by 60-80 % after delivery	Decreased to pre-pregnancy levels	[27]
Myocardial contractility	Increases for greater stroke volume	Increases	Continuing adaptation with maximal efficiency	Remains elevated	Generally, returns to normal	[28]
Left ventricular volume	Increased contractility	Moderate increase	Maximal state	Decreases	Returns to pre-pregnancy size	[29]
Left ventricular mass	Increases	Increases	Increases	Decreases	Decreases	[29]
Left atrial volume	Increases	Increases	Increases	Decreases	Decreases	[30]
Ejection fraction	Increases	Moderate decreases	Decreases	Decreases	Decreases	[31]
Hypercoagulable state	Increases	Increases	Increases	Remain elevated for 12 weeks	Gradually decreases	[32]

T3 and T4 production. Iodine, which is required for the creation of thyroid hormones, is also more in demand during pregnancy.<sup>34</sup> To avoid deficits that might negatively impact foetal development, maternal iodine consumption is therefore essential. Furthermore, the placenta generates enzymes that can break down thyroid hormones, so to keep levels sufficient, the mother must create more of them. Insulin resistance plays a crucial role in directing glucose toward the developing baby, guaranteeing a sufficient supply of nutrients for foetal growth.<sup>19</sup> The pancreatic  $\beta$ -cells adjust by becoming larger and more functional in order to make up for the increased insulin resistance. Together, hyperplasia and hypertrophy contribute to this adaptation by improving the pancreas's capacity to release insulin. In order to preserve glucose homeostasis, maternal blood insulin levels might rise by up to 75 % by the end of pregnancy.<sup>35</sup> Furthermore, pancreatic  $\alpha$ -cells have a role in pregnancy-related metabolic changes. Studies reveal an increase in  $\alpha$ -cell mass, linked to modifications in glucagon secretion that may impact maternal glucose levels.

The placenta's release of hormones such as hPL promotes the growth of  $\beta$ -cells and increases the generation of insulin.<sup>36</sup> GDM, which is characterised by hyperglycaemia from inadequate insulin production to counterbalance the increased insulin resistance, might result from the pancreatic  $\beta$ -cells' failure to adapt appropriately. Both the mother and the foetus are at danger from this disease, which may have long-term effects include raising the woman's postpartum risk of type 2 diabetes.<sup>37</sup> The embryo, endometrium, placenta and foetal membranes all create corticotropin-releasing hormone (CRH), which is essential for implantation, immunological regulation and shielding the foetus from the mother's immune system. Early in pregnancy, CRH levels at the implantation sites are much higher than in other regions, which affects T lymphocyte and trophoblast cell apoptosis.<sup>38</sup> The placenta is the primary source of CRH in plasma, which increases dramatically starting in the eighth week of pregnancy and affects uterine blood flow and maternal production of adrenocorticotrophic hormone (ACTH).<sup>39</sup> Additionally, oestrogenic levels rise, which impacts cortisol-binding globulin



and decreases cortisol breakdown. This results in a transient hypercortisolic condition.<sup>40</sup> Cortisol levels fall after giving birth and the hypothalamic-pituitary-adrenal (HPA) axis progressively reaches its pre-pregnancy state. While psychological stress does not have the same impact, lactating women exhibit decreased HPA responses to physical stress, which are probably caused by lower oestrogen and increased prolactin levels. Mother-infant emotional attachment is also influenced by CRH and the HPA axis.

## Maternal endocrine disorders and their aetiologies

Infants and toddlers are exposed to chemical pollutants not only during their intrauterine existence but also indirectly during their life. These poisons can damage the foetus via the placental cord and excrete via the meconium, impacting hormonal, neurological and immunological development.<sup>8</sup> Affected kids may be born with congenital defects and may suffer from health and behavioural difficulties throughout their existence. Endocrine disruptor levels in neonates' umbilical cord blood can define their exposure. Newborns are more vulnerable to environmental toxins than adults due to their underdeveloped metabolic pathways and their capacity to digest, detoxify and remove poisons. Exposures can often not be seen for many years, making some endocrine disruptor states of prenatal origin. Endocrine disruptors accumulate in fatty tissues due to their low water solubility and high lipid solubility, creating long-term consequences in later years.

### Pre-existing vs pregnancy-induced endocrine disorders

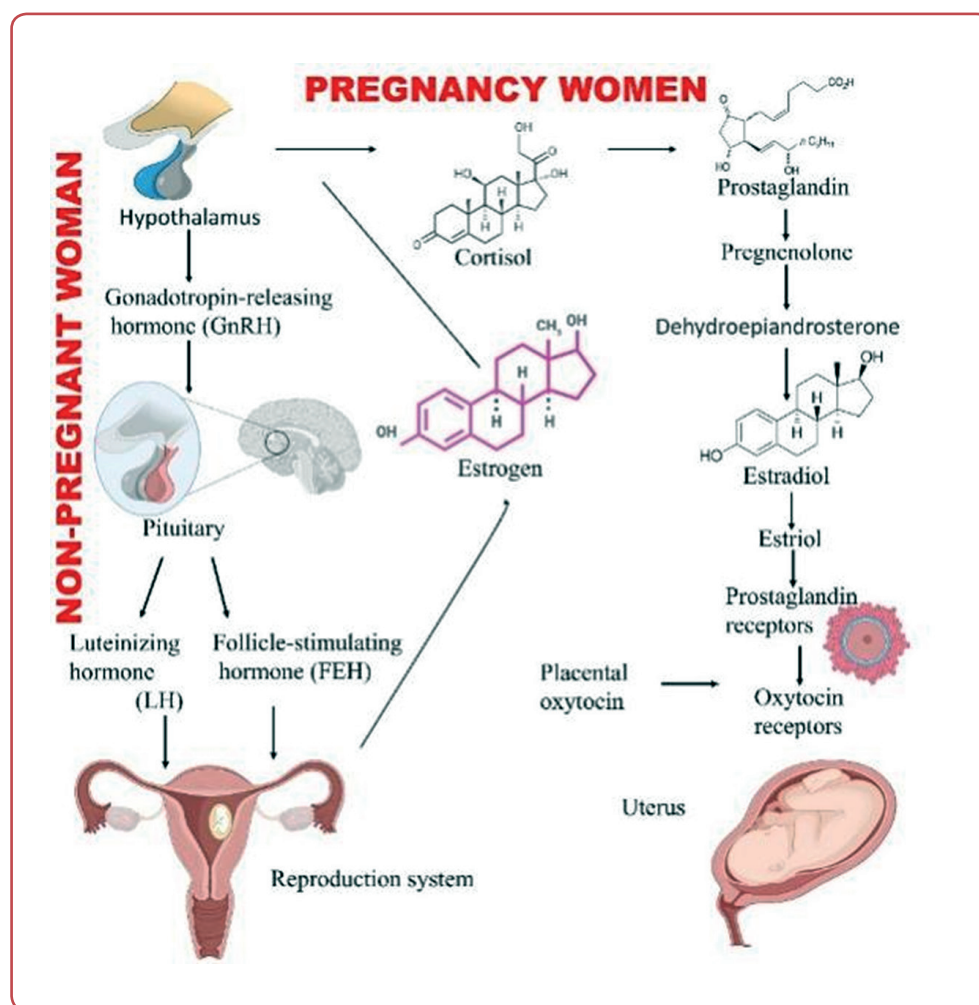
Pregnancy-unsuitable drugs may occur from co-existing hypertension, cardiovascular illness and renal disease in women with pre-existing diabetes. This may raise the chance of stillbirth, infant mortality and congenital abnormalities. Congenital anomaly rates are directly correlated with HBA<sub>1c</sub> in the first trimester.<sup>41</sup> Pregnancy with type I diabetes is five to six times more likely to result in pre-eclampsia than in the general population. Optimising blood pressure and glucose management, BMI and drug history are the goals of prenatal care. During the first trimester, a pre-existing diabetes complication assessment should be

conducted. Preventing pregnancy-related problems, detecting foetal structural heart defects and maximising glycaemic management are the main goals of antenatal care. Lower insulin needs and improves glycaemic management during the first trimester of pregnancy are linked to continuous insulin usage.<sup>42</sup> To prevent newborn hypoglycaemia, hourly blood sugar monitoring is part of intrapartum care. Insulin regimens ought to revert to their prenatal levels.

Thyroid illness is the second most prevalent endocrine problem in pregnancy, affecting up to 2-3 % of pregnancies.<sup>43</sup> The thyroid and adrenal glands control metabolism and stress reactions, whereas the pituitary gland controls hormones such as prolactin and growth hormone as shown in (Figure 1). Changes in maternal physiology, particularly the thyrotropic effect of hCG, which inhibits TSH and increases thyroid volume and hormone levels, create thyroid. Thyroid-binding globulin (TBG) is produced more often in the liver, which counteracts this and keeps levels within normal ranges.<sup>44</sup> It is generally known that neurodevelopmental problems including attention deficit hyperactivity disorder (ADHD) and seizure disorders are linked to brain abnormalities brought on by the mother's thyroid malfunction during pregnancy. While ADHD issues include morphological changes in the basal ganglia, cortical thickness and functional changes in dopaminergic, noradrenergic and serotonergic neurotransmission, seizure illnesses involve abnormalities of the cerebral cortex. The idea that maternal hypothyroidism during pregnancy may teach the unborn child to experience seizures later on is supported by research on both humans and animals.<sup>45</sup> Global thyroid hormone resistance caused by a mutation in the thyroid-receptor  $\beta$  gene is strongly linked to ADHD symptoms in people.<sup>46</sup> Children born to mothers who were first diagnosed and treated for thyroid disease in the years after pregnancy were more likely to have neurodevelopmental issues, according to Danish population-based study.

### Gestational diabetes mellitus (GDM): pathophysiology and risk factors

Pregnancy-related glucose intolerance caused by a combination of insulin resistance and  $\beta$ -cell malfunction is GDM. Hormonal changes during pregnancy, particularly from the placenta, lead to increased insulin resistance, which is necessary to provide an adequate glucose supply for foetal development. Failure of this hormone compensa-

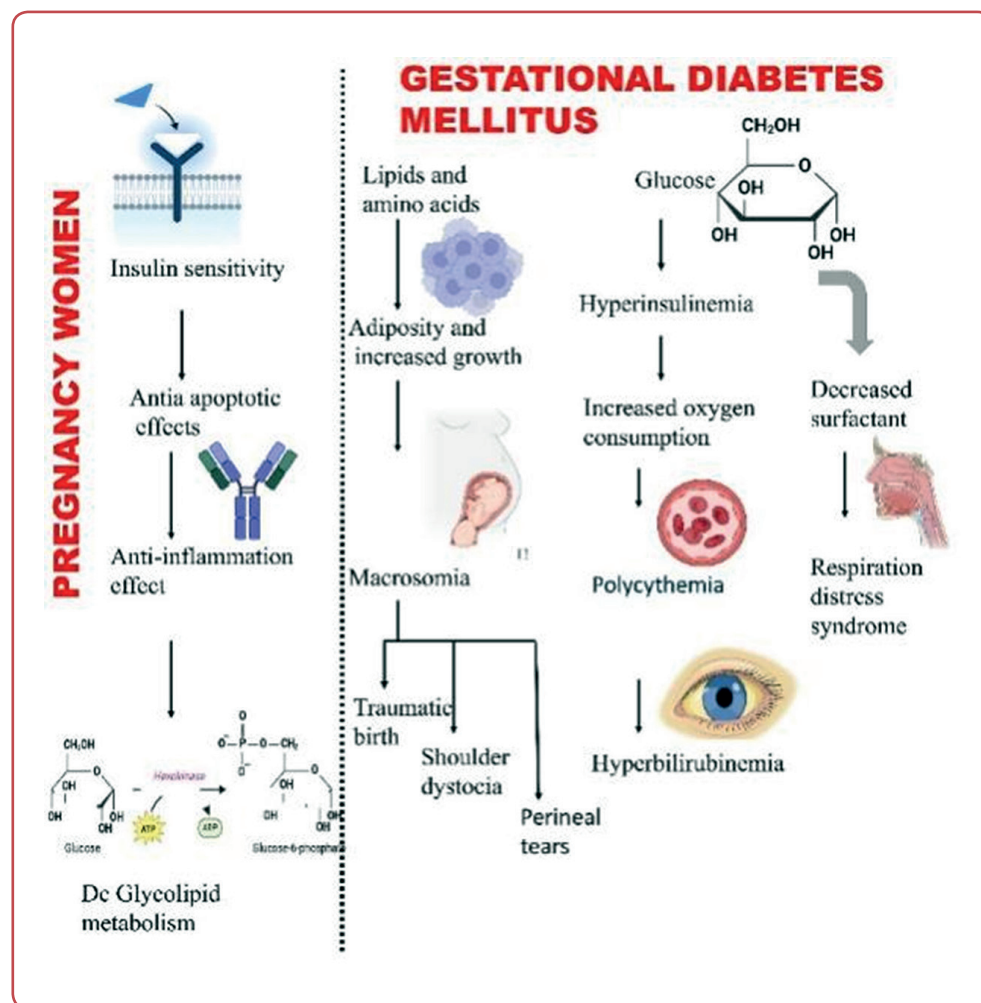


**Figure 1: Important endocrine organs during and after pregnancy**

The health of the mother and foetus depends on a few endocrine organs both during and after pregnancy. Hormones such as human chorionic gonadotropin (hCG), progesterone and oestrogen are produced by the placenta to aid in pregnancy. To sustain pregnancy, the ovaries discharge hormones and the pancreas modify insulin production. Postpartum menstrual cycles then resume. Following delivery, hormonal shifts persist, promoting nursing and recuperation.

tory response results in hyperglycaemia as shown in (Figure 2), which is a major health risk to the mother and the baby. GDM has a substantial effect on maternal endocrine health and increases the risk of cardiovascular disease and type 2 diabetes after childbirth.<sup>47</sup> Chronic inflammation and metabolic disorders before pregnancy may make these problems worse, suggesting that GDM frequently draws attention to underlying metabolic dysfunctions. In order to improve maternal and newborn outcomes and reduce the long-term health concerns associated with GDM, early diagnosis and monitoring are essential. Epidemiological studies have identified a number of risk factors for GDM, such as advanced maternal age, ethnicity, previous experience with GDM and a family history of type 2 diabetes.<sup>48</sup> These factors have a substantial impact on the development of GDM and women

over 40 have a more than twofold increased risk of developing GDM compared to women under 30. Geographical and racial differences in GDM prevalence have also been observed, with Asian women having the lowest rates and Filipino women having the highest.<sup>49</sup> Low plasma levels of vitamin D and vitamin C in the early stages of pregnancy and increased dietary fat consumption throughout pregnancy increase the risk of developing GDM.<sup>50</sup> Pregnancy diets that contain higher intakes of sugar, sweetened beverages, potatoes, fried foods, haem iron, animal fat and protein are also associated with an increased risk of GDM. However, from the sources about these risk factors before and throughout pregnancy, it is uncertain whether these behaviours have a long-term effect on insulin sensitivity and pancreatic  $\beta$ -cell function.



**Figure 2:** Pregnancy-induced vs pre-existing endocrine disorders

Hormonal changes during pregnancy cause pregnancy-induced endocrine diseases, which include gestational type 2 diabetes, pregnancy-induced hypertensive (PIH) and preeclampsia. These conditions often go away after giving birth. Pregnancy difficulties including miscarriage or preterm birth can be avoided by carefully managing pre-existing endocrine disorders, such as type 2 or 1 diabetes, thyroid illnesses and polycystic ovary syndrome (PCOS). Pre-existing illnesses may continue or worsen if they are not properly treated, even though pregnancy-induced disorders usually go away after birth.

## Polycystic ovary syndrome (PCOS) and fertility challenges

PCOS has a significant influence on maternal endocrine health, particularly cardiovascular disease (CVD) conventional risk factors, including hypertension, dyslipidaemia, diabetes and obesity, as well as non-classic risk factors, including homocysteine, C-reactive protein (CRP) and tumour necrosis factor- $\alpha$ , are more common in women with PCOS. Regarding the frequency of hypertension in women with and without PCOS, Brazilian research found that the illness was twice as common in PCOS-afflicted women. Insulin resistance and hyperinsulinemia, which are common in PCOS, change vascular smooth muscle cells, resulting in hypertrophy of the vascular muscle wall with decreased compliance and in-

terfere with endothelium-dependent vasodilation mechanisms, which appears to be the cause of the increased risk of hypertensive state.<sup>51</sup> Although PCOS is not a direct complication of pregnancy, its metabolic and endocrine abnormalities can predispose individuals to adverse pregnancy outcomes in the future. Increased insulin resistance and hyperinsulinemia are common in women with PCOS and these conditions may continue after conception and raise the risk of gestational diabetes, hypertensive and miscarriage in future pregnancies.<sup>52</sup> According to a group of research, women with PCOS may be more likely to develop breast and endometrial cancer. It has been shown that the anovulatory characteristics result in the endometrium's proliferative tissue proliferation, which eventually causes cancer. Other risk factors



for endometrial cancer include type 2 diabetes, obesity and insulin resistance, all of which are linked to PCOS.<sup>53</sup> The Study of Women's Health Across the Nation (SWAN), a longitudinal study of American women throughout menopause, looked at the relationship between PCOS symptoms and impaired glucose tolerance (IGT). IGT was more common in PCOS-afflicted women than in control women. Based on the history of oligomenorrhea throughout the reproductive years and the highest tertile of total testosterone levels, PCOS was assumed to be the cause. Women with PCOS are a high-risk category, since the annual incidence of DM development in the general population is 5.7 % for those with IGT at baseline.<sup>54</sup> It is essential in understanding the long-term endocrine implications of PCOS for optimizing preconception care and mitigating its impact on future pregnancy outcomes. As the prevalence of PCOS continues to rise, further research is necessary to develop targeted interventions to improve maternal and neonatal health.

## Impact of endocrine disorders on foetal development

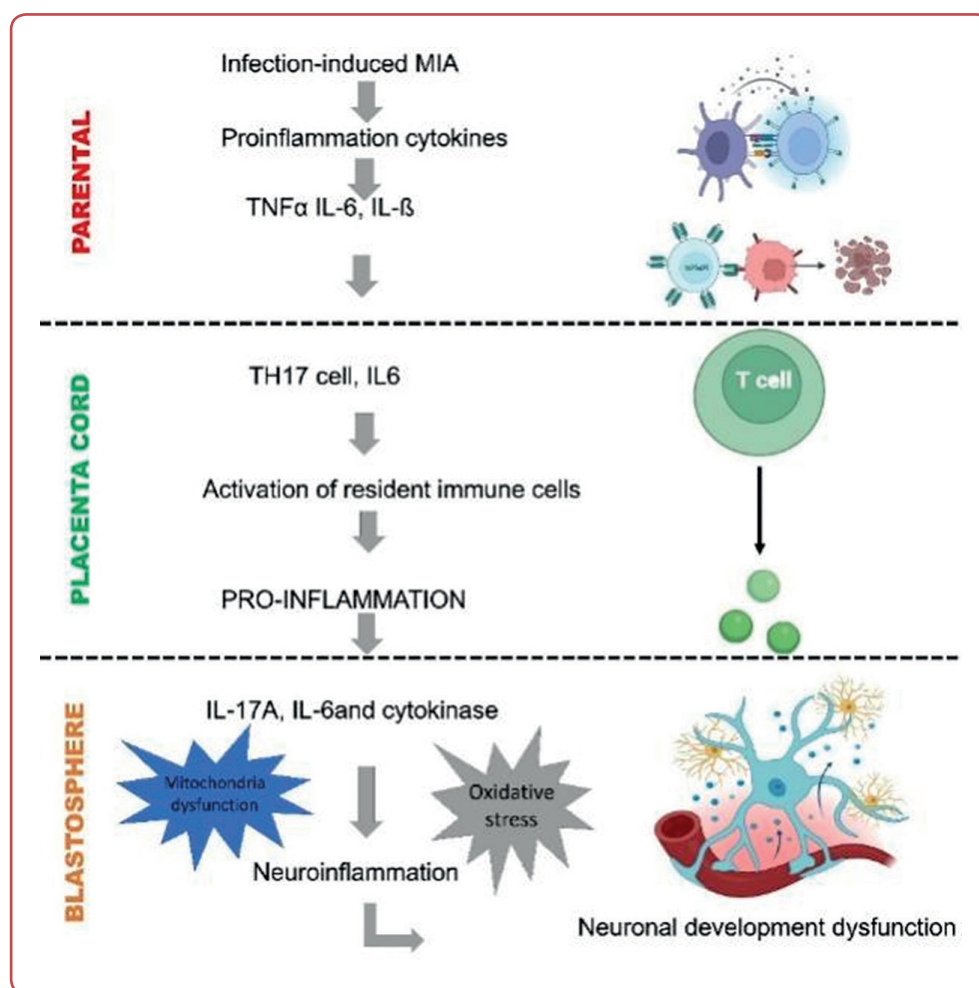
Infants and young kids are exposed to chemical pollutants not only during their intrauterine existence but also indirectly during their life. These poisons can damage the foetus via the placental cord and excrete via the meconium, impacting hormonal, neurological and immunological development. Affected offspring may be born with congenital defects and may suffer from health and behavioural difficulties throughout their existence. Endocrine disruptor levels in neonates' umbilical cord blood can define their exposure. Newborns are more vulnerable to environmental toxins than adults due to their underdeveloped metabolic pathways and their capacity to digest, detoxify and remove poisons.<sup>55</sup> Although exposures have occurred during foetal life or during the neonatal era, the effect of these exposures may sometimes not be recognised for many years, making some endocrine disruptor states of foetal origin. Endocrine disruptors accumulate in fatty tissues due to their low water solubility and high lipid solubility, creating long-term consequences in later years.

## Foetal neurodevelopment: effects of endocrine dysfunction

Hormone-regulated foetal neurodevelopment is a complex process that may be disrupted by endocrine disorders during pregnancy. Cognitive and neurological disorders may arise from this. It is well known that neurodevelopmental problems including ADHD and seizure disorders are linked to anomalies in the brain brought on by the mother's thyroid malfunction during pregnancy. The placenta's ability to transport nutrients and hormones to the foetus can be hampered by endocrine malfunction in mother, such as diabetes or thyroid disorders can lead to neurodevelopment dysfunction as showed in (Figure 3). Abnormal migration, proliferation, or synaptogenesis may lead to abnormalities of the cerebral cortex and seizures. Alterations in the hippocampus are also thought to be the cause of many types of seizures. Animal studies support the hypothesis that a mother's hypothyroidism during pregnancy may increase the risk of seizures in her foetus.<sup>56</sup> The neocortex was reorganised in offspring exposed to maternal hypothyroidism during pregnancy, as shown by aberrant migration and cytoarchitecture in the sensory cortex and hippocampus areas.<sup>57</sup> Furthermore, compared to rats not exposed to maternal hypothyroidism during pregnancy, offspring of exposed mothers were more likely to have seizures in response to an acoustic stimulation.

In addition to functional changes in dopaminergic, noradrenergic and serotonergic neurotransmission, neurodevelopmental abnormalities linked to ADHD include structural changes in the basal ganglia and cortical thickness in the frontal and parietotemporal regions. The symptoms of ADHD in humans have been closely linked to widespread thyroid hormone resistance brought on by a mutation in the thyroid-receptor  $\beta$  gene.<sup>58</sup> Cognitive development may be impacted by hypoglycaemia and compromised placental function, which may also reduce the quantity of glucose that reaches the embryonic brain. Together, altered hormone levels impact brain architecture, neural circuit formation and behaviour, leading to long-term neurodevelopmental impacts such difficulties with language, motor skills and social conduct. Studies demonstrating that even mild thyroid dysfunction in women may increase the risk of neurodevelopmental issues in their kids underscore the importance of maintaining normal hormone levels throughout pregnancy. Ad-





**Figure 3:** Endocrine dysfunction's effects on foetal neurodevelopment

Cognitive delays, behavioural problems and developmental difficulties may result from this disruption of embryonic brain development. Long-term neurodevelopmental repercussions may arise from maternal illnesses such as insulin resistance or elevated cortisol that further affect the foetus. L: Interleukin; TNF- $\alpha$ : Tumour necrosis factor-alpha;

ditionally, a failure in placental hormone production may lead to inadequate foetal growth and brain size, as seen in small-for-gestational-age (SGA) babies compared to average-for-gestational-age (AGA) fetuses.<sup>59</sup> Two hormones that are critical for the development of the foetal brain are prolactin and pregnancy-specific glycoproteins; poor neurodevelopment is linked to reduced production of these hormones as a consequence of placental dysfunction.<sup>60</sup> The hypothesis of pre-natal programming states that adverse maternal conditions, such as endocrine dysregulation, may increase the likelihood that children may have neurodevelopmental issues later in life. Even mild thyroid dysfunction in women may increase the risk of neurodevelopmental issues in their kids.<sup>61</sup>

## Endocrine disruptors and congenital defects

The primary cause of neonatal death, illness and long-term disability is congenital abnormalities. The main endocrine disruptors linked to reproductive issues include antiandrogens like phthalates, xenoestrogens like bisphenol-A (BPA) and polychlorinated biphenyls (PCBs). These substances may change reproductive development along a variety of locations, including the gonad and the hypothalamus, because of their mild steroid-like effect.<sup>62</sup> According to a number of studies, EDs may bind to hormone receptors, changing the genetic response. However, compared to natural oestradiol, the xenoestrogens that include phenol have binding affinities to the traditional nuclear hormone receptors that are at least 10000 times lower.<sup>63</sup> It is thus more like-

ly that small concentrations of these substances that are present in vivo influence their effect via non-genomic mechanisms or through other receptors and pathways. Xenoestrogens have been shown to bind to oestrogen receptors that are attached to cell membranes, activate secondary messenger kinases and affect calcium influx on many occasions.<sup>64</sup> Supplementing with folic acid during pregnancy is a rare preventive method that may reduce the risk of congenital defects and shield against environmental exposures.<sup>65</sup> To prevent congenital malformations, environmental factors such as occupation environment exposure should be included into preconceptional and prenatal treatment. It is crucial to limit expo-

sure to potential teratogens prior to pregnancy detection and this should be a component of primary care public health. It has been shown that periconceptional folic acid supplementation prevention is ineffective when women are targeted preconceptionally.<sup>66</sup> Given that many women go on to have many children, it may be challenging to develop effective preconceptional care strategies within the primary care framework. Prenatal screening and counselling should be part of prenatal treatment, however when addressing parental concerns, clinicians and counsellors should be aware of the uncertainties surrounding environmental contamination (Table 2).

*Table 2: Congenital anomalies arising from the occupational exposure*

Occupation	Study design	Exposure	Assessment method	Congenital anomaly	Effect on foetal development	Ref
Nurses	Case-control	Anaesthetics	Job-exposure matrix	Neural tube defects	Increased risk of developmental delays	[67]
Farmers	Case-control	Pesticides	Self-reported exposure	Congenital heart defects	Higher incidence of growth restriction	[68]
Factory workers	Cohort	Solvents	Industrial hygiene monitoring	Limb reduction defects	Impaired neurodevelopment	[69]
Hairdressers	Case-control	Hair dyes	Occupational history	Skin anomalies	Altered foetal growth patterns	[70]
Construction workers	Cohort	Heavy metals	Air sampling	Cleft lip/palate	Increased risk of cognitive deficits	[71]
Electricians	Case-control	Electromagnetic fields	Job-exposure matrix	Autism spectrum disorders	Delayed developmental milestones	[72]
Miners	Cohort	Diesel exhaust	Historical exposure assessment	Foetal growth restriction	Increased risk of preterm	[73]
Textile workers	Case-control	Chemical dyes	Expert assessment	Reproductive tract anomalies	Higher rates of miscarriage	[74]
Plastics manufacturing workers	Cohort	Phthalates	Biomonitoring	Neurodevelopmental disorders	Increased risk of behavioural issues	[75]
Welders	Case-control	Metal fumes	Self-reported exposure	Congenital heart defects	Higher incidence of learning disabilities	[76]
Healthcare workers	Case-control	Radiation	Dosimetry assessment	Childhood dosimetry assessment cancers	Increased risk of neurodevelopmental	[77]
Janitors	Cohort	Cleaning agents	Chemical exposure monitoring	Asthma in offspring	Increased respiratory issues in children	[78]
Transport workers	Case-control	Noise exposure	Noise level assessment	Hearing loss	Impaired auditory	[79]

## Impact of endocrine disorders on pregnancy outcomes

The health of both humans and animals is significantly jeopardised by the prevalence of endocrine disrupting compounds (EDCs).<sup>80</sup> These compounds are linked to chronic reproductive health issues in both men and women, where abnormal control of the reproductive system is common. In epidemiological studies, EDC exposure has been connected to various infertility and gestational complications, including preterm birth, reduced foetal growth, miscarriage and hypertension.<sup>81</sup> Both animal studies and human observations suggest that EDCs can adversely affect the quantity and quality of gametes, embryo fertilisation and the growth and development of foetal tissue and the placenta. EDCs primarily disrupt hormone-regulated processes critical to fertility and foetal development; they may also affect maternal immune responses, which can influence the likelihood of caesarean deliveries.<sup>82</sup> Since foetal and placental growth heavily relies on hormonal signalling, they are particularly susceptible to EDC disruptions.<sup>83</sup>

Research offers compelling evidence linking EDC exposure to various pregnancy-related issues. Clinical and epidemiological studies highlight associations between EDCs especially pesticides and plasticisers—and complications like preterm birth, restricted foetal development, preeclampsia, recurrent miscarriages and other common conditions affecting roughly 20 % of women.<sup>84</sup> It has been consistently observed that a diverse array of EDCs is present in biological samples from pregnant women, including urine, blood from the baby, plasma, amniotic fluid and breast milk. Exposure patterns can vary significantly, influenced by geographical, socioeconomic, occupational and lifestyle factors, which combine in numerous ways throughout pregnancy (termed the “exposome”).<sup>85</sup>

The placenta represents a critical site of EDC effects. This rapidly developing organ is highly responsive to hormonal regulation during morphogenesis and contains various hormone receptors to manage nutrient delivery to the foetus.<sup>86</sup> However, disruptions in hormone signalling can compromise this adaptability, leading to adverse effects on foetal growth and developmental programming.<sup>87</sup> Compounds such as triclosan and BPA have been shown to accumulate in maternal

tissues, affecting the synthesis and metabolism of placental hormones. *In vitro* studies reveal that numerous EDCs can directly impact trophoblasts, influencing signalling pathways that lead to genetic and epigenetic changes affecting cell survival and invasiveness.<sup>88</sup> Still, understanding the immediate versus maternal compartment impacts on trophoblasts requires further research on EDC effects in placental cells throughout pregnancy.<sup>89</sup>

## Preterm labour, stillbirth and neonatal complications

Even when provided with optimal nutrition, premature infants often experience slow growth and an increased tendency to accumulate excessive body fat. Our hypothesis posits that early maternal-placental-foetal separation disrupts the foetus's ability to maintain normal endocrine function, ultimately hindering postnatal development.<sup>90</sup> An infant's body composition is influenced by nutritional intake and hormone levels, which include those from the placenta, pituitary gland, thyroid, adrenal gland, pancreas and other tissues.<sup>91</sup>

## Lactogen from the human placenta

HPL is released in significant quantities into the mother's bloodstream between 32 to 35 weeks of gestation, reaching levels of 5000–7000 ng/mL. At term, lower concentrations of 20–50 ng/mL are also detected directly in the infant's blood.<sup>92</sup> Early in pregnancy, hPL has a minimal affinity for growth hormone receptors but exhibits a strong affinity for prolactin receptors found in the placenta, other maternal tissues and throughout the infant. HPL modulates maternal metabolism and elevates IGF-1 (insulin-like growth factor 1) levels, facilitating energy conservation for the foetus by inducing lipolysis and enhancing the absorption of free fatty acids.<sup>93</sup> This action increases substrate availability and transport, fosters placental development and function and indirectly supports foetal growth. Moreover, hPL encourages the foetus to produce more insulin and IGFs, aiding in growth and tissue differentiation.

## Glucocorticoids

Cortisol, the primary glucocorticoid, plays a crucial role in foetal growth and development. It is produced by the adrenal cortex in response to CRH from the hypothalamus and placenta.<sup>94</sup> Cortisol interacts with glucocorticoid receptors that are prevalent in mineralocorticoid-targeted tissues such as the kidneys, intestines, adrenal glands and placenta. Elevated cortisol levels are

often associated with stress and malnutrition, particularly protein deficiency.<sup>95</sup> Generally, cortisol inhibits growth by reducing IGF and leptin levels and decreasing pituitary growth hormone (GH) production in neonates. Nevertheless, cortisol promotes bulk tissue accumulation, allowing for the maturation of the foetus's organs and tissues. This mechanism makes physiological sense, as blocked IGF-1 production means that energy resources cannot be utilised effectively for growth.<sup>96</sup>

### Thyroid hormones

Thyroid hormones, particularly T3 and T4, are essential for healthy foetal and infant growth, especially for brain maturation. Observational studies have shown that they facilitate nervous system development, regulate metabolic rate and influence IGF-1 levels to support growth.<sup>97</sup> These hormones are responsible for the maturation of the heart, skeletal system and muscles. The presence of placental oestrogen and hCG stimulates maternal production of T3 and T4 during pregnancy and some maternal thyroid hormones can cross the placenta.<sup>98</sup> Delivering paternal thyroid medication to the developing embryo is crucial for early growth and may provide neurological protection against hypothyroidism, particularly as the foetus begins synthesising its own thyroid hormones around 20 weeks of postmenstrual age. Adequate thyroid hormones are vital for optimal postnatal development.<sup>99</sup>

### Growth hormone

GH has a direct affinity for growth plate receptors and actively promotes growth through various metabolic actions, such as stimulating development at the epiphyseal growth plate, encouraging lipolysis, fostering linear bone growth and enhancing lean mass accretion. However, during pregnancy, placental growth hormone (PGH) can inhibit the action of GH.<sup>100</sup> The growth-promoting impact on newborns, particularly preterm infants, is limited due to the immaturity of growth hormone receptors until around 6 to 9 months of life. Factors that influence GH production include leptin, somatostatin (which inhibits GH secretion), diet and growth hormone-releasing hormone.<sup>101</sup>

## Diagnostic approaches and monitoring

Pregnancy-related endocrine disorders are quite common, yet many pre-existing conditions can be effectively managed without significantly impacting maternal or perinatal health. However, if these disorders are inadequately controlled before conception or identified only during pregnancy, they may lead to adverse foetal outcomes and increased maternal morbidity.<sup>102</sup> Additionally, the transplacental passage of maternal antibodies can also negatively affect the foetus or newborn. One challenge in diagnosing endocrine disorders during pregnancy is the overlapping symptoms of normal pregnancy with symptoms that indicate specific endocrine pathologies. Furthermore, physiological changes during pregnancy can alter the reference ranges for common biochemical indicators, complicating initial diagnoses.<sup>20</sup> The intricate interplay between the fetoplacental system and the maternal endocrine system produces the extensive hormonal changes necessary for a successful pregnancy. These adjustments are crucial for the completion of pregnancy, childbirth and breastfeeding.<sup>103</sup> Pregnancy influences nearly every endocrine pathway, necessitating careful interpretation of biochemical test results that assess endocrine function. Due to the physiological changes that occur during this period, additional monitoring may be warranted during both prenatal and postnatal stages, especially since these changes can impact the clinical trajectory of pre-existing endocrine abnormalities, such as prolactinomas.<sup>104</sup>

### Biomarkers for maternal and foetal outcomes

Adiponectin (APN) is a hormone secreted by adipocytes in fat tissue, exerting significant effects on the liver and various organs. The structure of APN includes four domains: the N-terminal signalling peptide, a hypervariable region, collagen and a carboxy-terminal globular domain.<sup>105</sup> APN plays a critical role in regulating glucose and lipid metabolism; it enhances insulin sensitivity, promotes glucose uptake in peripheral tissues, limits glucose output and production and encourages the oxidation of plasma free fatty acids. Consequently, APN can reduce insulin resistance to some extent.<sup>106</sup> As insulin sensitivity improves, blood sugar levels decrease; conversely, rising blood glucose levels correlate with decreased insulin sensitivity, increased insulin resistance and lower APN levels.



Numerous studies have established a link between serum APN levels and GDM. Research involving 84 pregnant women showed that those with GDM had significantly lower serum APN levels compared to those without the condition.<sup>107</sup> Additionally, APN levels are a useful marker for monitoring blood glucose levels during pregnancy as given in and findings demonstrate that pregnant women with GDM exhibit markedly lower APN levels than those without the disorder. However, APN values can vary based on factors such as the duration of pregnancy, the severity of GDM, recent weight changes and even racial differences, suggesting that these aspects should be considered in early risk assessments.<sup>108</sup> Furthermore, APN also possesses anti-inflammatory and anti-apoptotic properties affecting blood vessels (Table 3).

Leptin is primarily produced and regulated by white adipose tissue. Its precursor consists of

167 amino acids, which includes a signal peptide of 21 amino acids. The precursor is cleaved to release leptin, a 146 amino acid peptide with a molecular weight of 16 KD.<sup>121</sup> When leptin binds to its receptors on pancreatic  $\beta$ -cells, it inhibits glucose-stimulated insulin secretion, leading to increased blood glucose levels. Numerous studies have highlighted a clear association between leptin levels and GDM. For example, a study by Yang identified elevated leptin levels in women with GDM, demonstrated that pregnant women with GDM presented significantly higher serum leptin levels.<sup>122</sup> These findings suggest that high leptin levels could serve as a predictive marker for GDM. Additionally, body mass index (BMI) is a key factor influencing leptin secretion; thus, it is essential to consider that overweight or obese pregnant individuals may have an enhanced number of adipocytes, which could further complicate islet function and potentially distort GDM predictions.<sup>123</sup>

**Table 3:** Showing some potential based biomarkers to improve maternal health outcomes and interventions

Biomarker	Type	Detection	Condition	Use	Merits	Demerits	Ref
C-reactive protein (CRP)	Inflammatory marker	Serum blood test	Gestational diabetes mellitus (GDM)	During pregnancy to assess inflammation levels	Indicates systemic inflammation; useful for monitoring	Non-specific	109
Interleukin-6 (IL-6)	Cytokine	Serum blood test	GDM, pre-eclampsia	Mid-to-late pregnancy for risk assessment	Predictive of complications	May not be specific to pregnancy	[110]
Tumour necrosis factor-alpha (TNF- $\alpha$ )	Cytokine	Serum blood test	GDM, pre-eclampsia	Mid-pregnancy for monitoring inflammatory status	Indicates inflammation; linked to adverse pregnancy outcomes	Non-specific	[111]
8-iso-prostaglandin F2 $\alpha$ (8-iso-PGF2 $\alpha$ )	Oxidative stress marker	Urine sample	Oxidative stress	Third trimester for assessing oxidative stress	Reflects lipid peroxidation associated with foetal growth	Requires careful timing of sample collection	[112]
Prostaglandin F2 $\alpha$ (PGF2 $\alpha$ )	Oxidative stress marker	Urine sample	Oxidative stress	Third trimester for evaluating oxidative stress	Indicates potential oxidative damage	Influenced by diet and lifestyle	[3]
Adiponectin	Hormone	Serum blood test	Gdm, obesity	Throughout pregnancy for metabolic health monitoring	Useful in metabolic assessment	Levels can be affected by obesity and inflammation	[113]
Insulin autoantibodies (IAA)	Autoantibody	Serum blood test	Type 1 diabetes	Early pregnancy for assessing autoimmune risk	Early detection of autoimmune diabetes in pregnancy	Limited availability in some labs	[114]
Thyroid hormones (TSH, FT4)	Hormones	Serum blood test	Thyroid dysfunction	First trimester for thyroid function assessment	Helps manage maternal thyroid health	Requires careful interpretation	[115]
Calcitonin	Hormone	Serum blood test	Medullary thyroid carcinoma	If there is suspicion of thyroid cancer during pregnancy	Useful as a tumour marker in thyroid cancer management	Not specific to pregnancy	

Phthalate metabolites	Environmental chemicals	Urine sample	Endocrine disruption	Early pregnancy for assessing environmental exposure risks	Association with adverse birth outcomes	Variability in exposure levels complicates interpretation	[117]
Oxidative stress markers (MDA, TAC)	Oxidative stress markers	Blood or urine samples	Pregnancy complications	Throughout pregnancy to monitor oxidative stress levels	Indicates oxidative stress levels and potential complication	Interpretation complex due to multiple influencing factors	[118]
Foetal growth factors (IGF-1, IGF-2)	Growth factors	Serum blood test	Foetal growth restriction	Mid-pregnancy for evaluating foetal growth potential	Important for assessing foetal growth and development	Levels can be influenced by maternal factors and conditions	[119]
MicroRNAs (miRNAs)	Non-coding RNA	Blood or tissue samples	Various endocrine disorders	Research settings and potential future diagnostics	Emerging biomarkers for disease prediction and monitoring	Standardisation needed for clinical use	[120]

C-reactive protein (CRP) is a protein produced by the liver that responds swiftly to inflammation, peaking at approximately eight hours post-injury or infection. Elevated CRP levels are associated with conditions such as infections, inflammation, burns and late pregnancy.<sup>124</sup> CRP acts by opsonising pathogens and damaged tissue, facilitating their elimination through immune responses. High blood levels of CRP are indicative of chronic inflammation and may relate to insulin resistance (IR) and cardiovascular disease across both genders. In pregnant women, particularly those at risk for GDM, an imbalance in lipoprotein levels can promote chronic inflammation of the vascular endothelium, driving an increase in CRP levels. Such chronic inflammation can further disrupt blood glucose metabolism, potentially contributing to dysglycolipid metabolism and, consequently, GDM.<sup>125</sup>

Research consistently shows a strong connection between GDM and CRP levels. For instance, studies indicate that elevated CRP levels during early pregnancy correlate with an increased likelihood of GDM and serum CRP levels were significantly higher in the GDM group compared to healthy controls.<sup>126</sup> Amirian's findings further support the notion that CRP may be a reliable marker for predicting GDM. The ROC curve analysis in various studies indicates that CRP levels greater than 1.86 g/mL effectively predict adverse pregnancy outcomes, underscoring the significance of elevated CRP levels as a potential indicator of GDM, with higher concentrations suggesting an increased risk of developing the condition.<sup>127</sup>

### Advances in imaging and non-invasive prenatal testing

Prenatal diagnostics play a crucial role in reducing the incidence of genetic disorders, which can greatly affect the psychological and financial well-being of individuals and their families, as well as place a substantial burden on healthcare systems. The classification of Down syndrome under trisomy sparked extensive research into chromosomal abnormalities, leading to the discovery of smaller genetic defects and various single gene disorders over the years. The most recent advancements in prenatal diagnosis empower expectant parents to make informed decisions regarding their unborn children while aiding healthcare professionals in managing pregnancies and providing appropriate counselling.<sup>120</sup>

In the 1960s, significant investigations focused on the potential applications of amniotic fluid cytology for determining foetal sex and conducting karyotyping. It wasn't until the 1980s that chorionic villus sampling (CVS) became a technique used for foetal karyotyping. Since then, CVS and amniocentesis have become popular methods for detecting genetic abnormalities in fetuses. Historically, the primary drawbacks of these invasive techniques have been the risks associated with the procedures and the potential for surgical loss of the pregnancy.<sup>9</sup>

To reduce the reliance on invasive methods, the scientific community has been pursuing non-invasive screening options to identify women who may be at higher risk of having fetuses with aneuploidies for the past five decades. In the 1960s, maternal age was the main predictor for invasive

procedures; however, when used in isolation, it had a high false-positive rate (FPR) of around 15 % and a relatively low sensitivity of 30 %. Although older mothers are at increased risk for trisomies (such as T21, T13 and T18), age alone does not necessarily indicate additional risks for other aneuploidies, including triploidy or sex chromosomal aneuploidies.

The discovery of biochemical markers related to foetal aneuploidies led to the development of two distinct screening methods: the triple test and the quadruple test. A recent review involving over 108,000 combined screening tests demonstrated detection rates (DRs) of 90 % for T21, 97 % for T18 and 92 % for T13 at a 4 % FPR. Nearly fifty years ago, it was established that foetal nucleated cells could be detected in a mother's bloodstream despite the presence of the blood-placental barrier. Research indicates that this cellular content increases with gestational age and is rapidly cleared at the end of pregnancy, making it suitable for pregnancy testing.

The field has made significant strides with the introduction of non-invasive prenatal testing (NIPT), particularly highlighted in 2008 when it was shown that maternal plasma could be examined for T21 with a very low FPR using circulating cell-free DNA (cff-DNA) sequencing. A simple blood sample from the expectant mother allows for the analysis of cff-DNA, with over 2 million NIPTs performed since the program's inception in 2011.<sup>128</sup>

As genetic testing technologies continue to advance, there is a rising demand for assurance regarding the health of children, regardless of whether pregnancies result from *in vitro* fertilisation or spontaneous conception. To reduce the risk of recessive disorders prior to conception, genetic tests to determine a couple's carrier status have also been developed. Additionally, analysing blastocyst DNA before embryo implantation offers another avenue for genetic assessment. It is important to note that preconceptional testing, like NIPT, is not meant to replace pregnancy testing during the prenatal period.<sup>129</sup>

## Future directions

While some statistics on the incidence and trends of developmental anomalies in male reproduction may not be entirely reliable, there is a broad consensus that these issues are relatively common and appear to be on the rise in certain regions. Among the most prevalent congenital conditions are cryptorchidism and hypospadias, which affect approximately 2 to 5 % of boys, with many needing surgical intervention. Additionally, poor semen quality is recognized as a significant contributor to infertility in couples, impacting about 6 to 8 % of men. Testicular tumours also rank among the most diagnosed cancers in young males, with a lifetime risk estimated between 0.3 % to 0.8 % across many countries. Despite these concerning trends, male reproductive and sexual health research receives considerably less attention and funding compared to female reproductive health.

These conditions have been theorised to be linked within a group of disorders referred to as "testicular dysgenesis syndrome," which is thought to originate during foetal development. Research has increasingly focused on understanding the mechanisms at play during this critical period. It has become evident that reduced testosterone production and action are significant contributors to testicular dysgenesis syndrome; however, it is essential to recognize that this condition may merely reflect secondary symptoms of an underlying disruption, such as inadequate differentiation of Sertoli cells, Leydig cells, peritubular myoid cells and immature germ cells, leading to functional impairments.

There could be multiple pathways contributing to this phenomenon. As research progresses, we anticipate discovering more about the complex relationships between diet, energy metabolism and reproductive function. Advances in genetic techniques are also enabling the identification of specific genomic regions that appear to increase risk, offering further insights into the aetiology of these developmental anomalies in male reproduction.

## Conclusion

Exposure to endocrine-disrupting chemicals can significantly impact fetoplacental growth and affect pregnancy outcomes through various pathways. Many EDCs, particularly steroidal compounds that mimic oestrogen, can quickly penetrate cellular membranes to influence gene transcription and travel into the nucleus. These endocrine disruptors may contribute to infertility in both men and women by altering the secretion of gonadotropin-releasing hormone from the hypothalamus, stimulating pituitary proliferation, triggering early puberty and interfering with the endocrine functions of the hypothalamic-pituitary axis. Moreover, the epigenetic imprinting of steroidogenesis and organogenesis within the uterus can pose risks to the gonadal programming of the offspring.

One of the most encountered EDCs is BPA, which has been linked to obesity by disrupting normal metabolic processes and predisposing individuals to overweight and obesity. This is particularly concerning, as obesity and excess weight can complicate pregnancy and negatively affect maternal and foetal health.

It is critical to recognise that the presence of EDCs represents a serious threat to human health, especially during pregnancy. Pregnant women are often exposed to high levels of EDCs through their diet and other environmental factors, rendering them especially vulnerable. The biological properties of EDCs enable them to cross the placental barrier and reach the developing embryo, potentially leading to abnormal genetic and epigenetic regulation. These alterations can be sex-specific and may contribute to complications related to placental development and pregnancy.

However, there remains much for the medical and scientific community to uncover regarding the mechanisms by which EDCs influence physiological processes during pregnancy. A primary limitation contributing to the varying findings in the existing literature is the considerable diversity in models and experimental designs utilised to examine EDC activity during the perinatal stage. To enhance the reliability of the data, researchers in this field must strive to establish standardised protocols and norms to ensure consistency and accuracy in future investigations.

## Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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## Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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